the cancelled claim. Support for this amendment may be found in claim 33 as filed. None of these amendments adds new matter. Applicant requests entry of the amendments.

Rejection Under 35 U.S.C. §112, First Paragraph

The specification is objected to and claims 1-5 and 32-36 stand rejected under 35 U.S.C. §112, first paragraph as "failing to provide an adequate written description" and "failing to teach how to make and use the claimed invention," i.e., as "failing to provide an enabling disclosure." Specifically, the Examiner contends that "it is not clear from the specification whether $\alpha_4\beta_1$-specific antibodies can inhibit lymphocyte adherence or migration in humans .... Therefore it does not appear that the asserted operability of the claimed method and compositions for inhibiting lymphocyte adherence and migration in vivo in humans would be enabled in view of the contemporary knowledge in the art." Applicant traverses.

Applicant discovered and disclosed in this application that $\alpha_4\beta_1$, a molecule on the surface of lymphocytes also known as VLA4, mediates the non-tissue specific adhesion of lymphocytes to endothelial cells. Claims 1-5, 32 and 34-36 are directed to methods of inhibiting such adhesion using anti-$\alpha_4\beta_1$ antibodies.

Claims 1-5 recite methods of inhibiting lymphocyte adhesion to endothelial cells comprising exposing lymphocytes to an antibody that binds to $\alpha_4\beta_1$. Claims 32-36 recite methods for preventing the migration of lymphocytes into tissues by administering an antibody that prevents the adhesion of lymphocytes to endothelial cells via $\alpha_4\beta_1$.

The Court of Appeals for the Federal Circuit has reviewed the requirements of 35 U.S.C. § 112, first paragraph,

for pharmaceutical inventions in In re Brana, 51 F.3d 1560, 34 USPQ2d 1437 (Fed.Cir. 1995). According to the Court, the Patent Office has the initial burden of challenging the presumptively correct assertion of utility in the disclosure by providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. Unless this initial burden is met, applicants should not be required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of § 112. Brana, 51 F.3d at 1566, 34 USPQ2d at 1441.

To decide if the initial burden was met, the Court in Brana considered the references cited by the Examiner and the nature of the invention. Because the cited references discussed only the therapeutic predictive value of *in vivo* animal tests of antitumor agents but did not question the usefulness of the compound as an anti-tumor agent, the Court concluded that the references would not cause one of skill in the art to question the utility of the compounds. The identical conclusion follows from the references cited by the Examiner in this application.

None of the documents cited by the Examiner provides evidence that one of skill in the art would doubt the *in vitro* or *in vivo* ability of anti-adhesion molecule antibodies in general, or anti-$\alpha_4\beta_1$ antibodies in particular, to inhibit lymphocyte binding to endothelial cells. Indeed, the references relied on by the Examiner discuss only the development of human treatments exploiting that ability. They do not challenge, and in fact support, the underlying activity of the antibodies.

Waldmann, Harris, Mountain, Ward, Shaffer, and Jolliffe review antibody-based and adhesion molecule-based anti-inflammatory therapies. They refer to side effects in the clinical use of rodent antibodies (such as immunogenicity),

particularly where repeated doses are required. They also describe various approaches to avoiding those side effects including engineering humanized antibodies, producing human antibodies or co-administering immunosuppressants. They never suggest that the antibody does not work.

Brennan reviews studies using animal models to investigate the role of cytokines in various stages of arthritis. Brennan states that the results observed in animal models correlated well with observations of the disease in humans and that the models are "clearly useful" (page 2, Conclusions). Brennan merely cautions that there are limitations on the interpretation of results from animal models of arthritis due to the rapid course of the disease in animal models (Id.). Again, there is no suggestion in Brennan that the model can never be used or is never predictive.

Kahan is directed to a general discussion of immunotherapies in organ transplantation. Kahan, like the other cited references, notes the immunogenicity of rodent antibodies in humans (page 555-556). It also describes alternative immunosuppressive regimens to avoid such side effects (pages 556-558). Kahan notes that "no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy" and thus that dose extrapolation is not possible from *in vitro* systems. Nowhere does Kahan state that antibodies do not inhibit lymphocyte-endothelial cell binding *in vivo*.

Edgington is directed to inflammation therapies using carbohydrates, particularly sLe^x, and notes that immunosuppressive therapies in general will require further development. Edgington does not even address the use of antibodies for anti-inflammatory therapy.

It is implicit in all of the above documents that anti-adhesion molecule antibodies are operable *in vivo*. Otherwise, there would be no point in modifying the antibodies for human treatment. In fact, many of the cited references specifically note the successful *in vivo* use of anti-adhesion molecule antibodies. For example, Mountain states that "mAbs have already been used clinically ... for the modulation of immune responses" (page 1). Kahan states that "prophylactic and therapeutic administrations of a mAb directed against human ICAM-1 delayed the onset and progression of renal allograft rejection in primates and mouse, anti-LFA-1 reversed certain graft versus host reactions in man" (page 557, right column). Schaffer reports that "responses have been encouraging" with the use of anti-ICAM mAbs in patients with arthritis (page 9, right column). Jolliffe states that "there are a number of mouse monoclonal antibodies to human antigens that have been shown to be efficacious in animal models of human disease and have the potential to provide needed clinical benefit" (page 242).

The Court in Brana also considered whether the nature of the invention alone would cause one of skill in the art to reasonably doubt its usefulness. The Court concluded that treating cancer with chemical compounds did not suggest "an inherently unbelievable undertaking or involve implausible scientific principles" so as to cause such doubt. In re Brana, 51 F.3d at 1566, 34 USPQ2d at 1441.

For the same reasons, the nature of applicant's invention would not cause the skilled worker to ignore the references and to doubt the asserted operability. Preventing $\alpha_4\beta_1$-mediated lymphocyte binding to endothelial cells by blocking $\alpha_4\beta_1$ on the surface of lymphocytes with $\alpha_4\beta_1$-specific antibodies is not inherently unbelievable. Nor are the

scientific principles involved in the use of anti-$\alpha_4\beta_1$ antibodies to block $\alpha_4\beta_1$-mediated binding implausible.

Additionally, applicant's claims are patentable under § 112, first paragraph for the following reasons. First, the methods of claims 1-5 are specifically exemplified in the application. The specification describes an adhesion assay in which human umbilical vein endothelial cells (unactivated and activated with IL-1ß or TNF-ß) are incubated with labelled lymphocytes, in the presence or absence of various antibodies. Monoclonal antibodies directed against $\alpha_4\beta_1$, but not against other VLA proteins, inhibited human lymphocyte adhesion to human endothelial cells (page 50, lines 12-34 and Table IX). Because the adhesion step is necessary for migration into tissues, anti-$\alpha_4\beta_1$ antibodies also block lymphocyte migration.

Second, with the September 14, 1994 Response, applicant provided T. A. Yednock et al., "Prevention of Experimental Autoimmune Encephalomyelitis by Antibodies Against α4ß1 Integrin," Nature, 356, pp. 63-66 (1992) ("Yednock"). Yednock demonstrates that the anti-α_4 antibody, HP2/1, was effective in suppressing the immune response in an art-accepted rat model for multiple sclerosis. The Examiner's response to this showing was that "multiple sclerosis is one of the most difficult diseases in which to judge the effect of therapy since its natural history is unpredictable." The Examiner has misunderstood applicant's purpose in citing Yednock. Applicant provided Yednock as evidence to confirm that the methods of the invention are operable *in vivo*, not as proof of the successful treatment of multiple sclerosis.

Applicant submits herewith R.R. Lobb and M.E.Hemler, "The Pathophysiological Role Of α_4 Integrins In Vivo," J. Clin. Invest., 94, pp. 1722-1728 (1994) (copy enclosed), which reviews

numerous other *in vivo* studies supporting the same conclusion - that anti-VLA4 antibodies block leukocyte adhesion *in vivo*.

In the absence of information in the art that would lead a skilled artisan to doubt the operability of the methods of the invention, and in view of the evidence confirming the asserted *in vivo* operability of anti-$\alpha_4\beta_1$ antibodies in animal models, the application meets the requirements of § 112, first paragraph.

This conclusion is in accord with the holding of the Federal Circuit in Brana, that proof of *in vivo* human efficacy was not required to meet the requirements of § 112, first paragraph:

> "The commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption.
>
> * * * *
>
> "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer" Brana, 34 USPQ2d at 1442-1443.

In view of the above, applicant requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 34-36 are rejected under 35 U.S.C. § 112, second paragraph as "indefinite." Specifically, the Examiner asserts that claims 34-36 lack proper antecedent basis since they depend from a cancelled claim. Applicant has amended claim 34 to indicate its dependency from claim 32. Thus, claim 34 and

claims 35 and 36 which depend from it, have proper antecedent basis.

Rejection Under 35 U.S.C. § 102(e)

Claims 1, 2, 32 and 34 are rejected under 35 U.S.C. § 102(e) as anticipated by United States patent 5,403,919 (E.C. Butcher)("Butcher"). Specifically, the Examiner contends that "Butcher teaches the in vivo inhibition of leukocyte-endothelial interactions and leukocyte extravasation by the MEL-14 monoclonal antibody....The MEL-14 antibody binds the α^4 component of the claimed $\alpha_4\beta_1$ specificity." Applicant traverses.

Claims 1, 2, 32 and 34, as amended, recite methods for inhibiting the adherence of lymphocytes to endothelial cells other than those lining HEV and for preventing lymphocyte migration into tissues using an antibody that binds to $\alpha_4\beta_1$.

A rejection for anticipation under section 102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. In re Paulsen, 30 F.3d 1475, 1478-79 (Fed.Cir. 1994); Scripps Clinic & Res. Found. v. Genentech, Inc., 927 F.2d 1565 (Fed.Cir. 1991). Under this well-settled legal standard, Butcher cannot support a § 102 rejection of applicant's claims does not do this.

Contrary to the Examiner's assertion, Butcher does not disclose that the MEL-14 antibody binds to $\alpha_4\beta_1$. Butcher suggests that MEL-14 defines a lymphocyte surface receptor in the mouse (Col. 2, lines 2-7). Butcher also suggests that MEL-14 antigen, like the Hermes-1 antigen has an apparent molecular weight of about 90,000 (Col. 2, lines 7-43). However, the murine homing receptor defined by MEL-14 is $gp90^{MEL-14}$, not $\alpha_4\beta_1$, which is an integrin having a molecular weight of about 280,000

(Hemler, p. 4, lines 22-23). In response to a request from applicant's attorney Jane Gunnison, the Examiner pointed to Holzmann, *infra*, as disclosing such binding. However, Holzmann also states that MEL-14 "recognizes a branched-chain ubiquitinated lymphocyte cell-surface glycoprotein with an apparent molecular weight of 90,000 (citations omitted)" (page 45). Accordingly, if the Examiner maintains this rejection, applicant requests that he provide evidence of MEL-14 binding to $\alpha_4\beta_1$. In the absence of such evidence, Butcher cannot anticipate applicant's invention.

Rejection Under 35 U.S.C. § 103

Claims 1-5, 32 and 34-36 are rejected under 35 U.S.C. § 103 as "unpatentable" over Butcher, in view of European Patent EP-0-330506 (M. E. Hemler et al.)("Hemler") and Y. Takada et al., "Fibronectin Receptor Structures In The VLA Family of Heterodimers," Nature, 326, pp. 607-609 (1987) ("Takada"). Specifically, the Examiner contends: (1) that Butcher teaches methods to control leukocyte extravasation by inhibiting leukocyte-endothelial interactions with adhesion molecule-based antibodies and the *in vivo* inhibition of such interactions by MEL-14 monoclonal antibody; (2) that Hemler teaches the structure of VLA antigens, the importance of $\alpha_4\beta_1$ in leukocyte adhesion during inflammation and that VLA proteins can interfere with cell attachment mechanisms and immune cell function; and (3) that Takada teaches the importance of β_1 in leukocyte adhesion and the ability of anti-β_1 antibodies to block cell adhesion to matrix proteins. The Examiner concludes that "one of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of inhibiting leukocyte-endothelial adhesion and leukocyte

extravasation, as taught by Butcher with $\alpha_4\beta_1$-specific antibodies, as taught by the combined references, as therapeutic agents in treating inflammatory reactions, as taught by Butcher and Hemler et al." Applicant traverses.

Applicant's invention relates to methods of intervening in lymphocyte migration into tissues in response to inflammatory stimuli. Specifically, applicant's invention is directed to methods of blocking the adhesion of lymphocytes to inflamed blood vessel endothelial cells.

In contrast, Butcher relates to lymphocyte adhesion during homing. Homing is the tissue specific migration of lymphocytes into lymphoid tissue where they develop antigen specificity. Butcher relates to molecules on the surface of specialized endothelial cells in lymphoid tissue and to monoclonal antibodies directed against those surface molecules. According to Butcher, such monoclonal antibodies inhibit lymphocyte binding to high endothelial venules ("HEV") in peripheral lymph nodes and Peyer's patches. Butcher provides no teaching about adhesion molecules involved any other lymphocyte binding. Nor does Butcher make any reference to $\alpha_4\beta_1$ or to anti-$\alpha_4\beta_1$ antibodies.

The Examiner points to references in Butcher to previous studies reporting the inhibition of lymphocyte migration in murine peripheral lymph nodes by MEL-14 (col. 2, lines 2-7 and 36-65). As discussed *supra*, MEL-14 is not known to bind to $\alpha_4\beta_1$. Further, Butcher states that the antigen defined by MEL-14 is expressed on neutrophils (col. 2, lines 36-43 and 62-65). It is known that $\alpha_4\beta_1$ is not expressed on neutrophils. Thus, Butcher contains no teaching or suggestion of the involvement of $\alpha_4\beta_1$ in lymphocyte adhesion to endothelial

cells. Neither of the other cited documents, either alone or together, cure this defect.

Hemler relates to the isolation and purification of VLA proteins. Specifically, Hemler refers to the isolation of VLA4 from T-lymphoblastoid and T-leukemic cell lines using anti-α_4 and anti-β_1 antibodies. Hemler refers to autoimmune disorders characterized by activated T cells with increased expression of some VLA proteins. Hemler also refers to the use of antibodies directed against VLA proteins to diagnose and evaluate such disorders. Hemler makes no reference to lymphocyte adhesion to other cells. In fact, Hemler teaches a different function for VLA4 -- adhesion to the extracellular matrix, a substrate layer associated with some tissues (page 2, lines 7-8). Hemler suggests that VLA proteins "inhibit cell binding to matrix proteins such as collagen, fibronectin and laminin" (page 5, lines 26-27). Thus, Hemler teaches away from applicant's discovery -- the cell-cell adhesion role of VLA4. Nothing in Hemler teaches or suggests that any VLA protein, much less VLA4, has a function in lymphocyte adhesion to endothelial cells. Hemler, thus, provides no motivation to evaluate the efficacy of anti-VLA4 antibodies to inhibit such adhesion.

Takada adds nothing to the teachings of Butcher and Hemler. Takada refers to studies done to determine whether VLA proteins mediate cell adhesion to matrix proteins. Takada refers to the cross-reactivity of anti-fibronectin receptor antibodies with the common ß unit of VLA proteins. Takada makes no reference to immune responses or to lymphocyte binding to endothelial cells. Instead, Takada merely states that the studies "confirmed that at least some of the widely distributed VLA proteins of previously unknown function are involved in cell adhesion to fibronectin and laminin" (page 607, Abstract).

Takada adds that because antibodies directed against the common ß subunit of VLA proteins blocked binding to fibronectin and laminin, all VLA heterodimers may have related functions, i.e., binding to matrix proteins. Thus, like Hemler, Takada teaches away from applicant's invention.

As none of the cited references, either alone or in combination, teaches or suggests that $\alpha_4\beta_1$ is involved in lymphocyte adhesion to endothelial cells, they cannot render obvious applicant's invention.

Claims 3 and 35 are rejected under 35 U.S.C. §103 as unpatentable over Butcher, in view of Hemler and Takada, and further in view of B. Holzmann and I.L. Weissman, "Integrin molecules Involved in Lymphocyte Homing to Peyer's Patches," Immunological Reviews, 108, pp. 45-61 (1989) ("Holzmann"). The Examiner asserts that Holzmann teaches the importance of $\alpha_4\beta_1$ in leukocyte adhesion and that α_4-specific antibodies (including P4C2) inhibit human leukocyte-endothelial cell adhesion. The Examiner concludes that one of skill in the art would have been motivated to select and evaluate the efficacy of inhibiting leukocyte-endothelial adhesion and extravasation as taught by Butcher with $\alpha_4\beta_1$-specific antibodies as taught by the combined references, with a reasonable expectation of success in producing the claimed invention. Applicant traverses.

As discussed above, Butcher, Hemler and Takada provide no teaching whatsoever as to the role of $\alpha_4\beta_1$ in lymphocyte adhesion to endothelial cells.

Holzmann relates to molecules involved in lymphocyte homing to Peyer's Patches. Specifically, Holzmann refers to LPAM-1 ($\alpha_{4m}\beta_p$) and LPAM-2 ($\alpha_{4m}\beta_1$) which appear to be involved in lymphocyte binding to murine Peyer's patch HEV. Holzmann refers to an apparent homology between murine LPAM-2 and human VLA4 and

refers to data that appear to show the inhibition of lymphocyte binding to murine Peyer's patch HEV by anti-α_4 antibodies.

One of skill in the art would recognize that any teachings in Holzmann are confined to a very narrow context -- lymphocyte homing to Peyer's patch HEV -- and thus have no bearing on events during inflammatory responses, to which applicant's invention relates. Applicant's invention, in fact, relates to an entirely different biological process, in different tissues and organs and involving different cells than Holzmann.

First, lymphocyte homing, referred to in Holzmann, is distinct from lymphocyte adhesion and extravasation during immune reactions. Homing occurs only in lymphoid tissue where lymphocytes are exposed to diverse antigens. Immune reactions, on the other hand, occur in any tissue or organ in response to inflammatory stimuli. Holzmann, in fact, makes no reference to adhesion events in inflammatory reactions.

Second, lymphocyte homing is itself organ specific. Holzmann states that:

> "[a]t least three antigenically and functionally distinct lymphocyte-HEV recognition systems controlling the homing of lymphocytes to peripheral lymph nodes, mucosal lymphoid organs (Peyer's patches, appendix) and inflamed synovium have been identified" (citations omitted)(page 45).

Holzmann is directed to only one of these systems -- homing to Peyer's patches. According to Holzmann, LPAM-1 and LPAM-2 are not involved in lymphocyte homing to other lymphoid organs (page 47, second paragraph). Holzmann, in fact, postulates that LPAM-2 (the purported murine homologue of human VLA4) is part of the organ-specific component of a lymphocyte receptor system for mucosal HEV (pages 56-57). As a result, Holzmann provides no suggestion that VLA4 is generally involved in lymphocyte adhesion in any other tissue or organ.

Finally, Holzmann relates to the even narrower context of lymphocyte adhesion to HEV within Peyer's patches. It was known at the time Holzmann was published that homing lymphocytes bind to HEV but not to other blood vessels in the same organ. See M. Gallatin et al., "Lymphocyte Homing Receptors," Cell, 44, pp. 673-680 (1986) (copy enclosed) ("[R]ecirculating lymphocytes adhere only to HEV and not to other blood vessels, either in lymphoid organs or in other types of tissues" (page 673)); and H.B. Stamper, Jr. and J.J. Woodruff, "Lymphocyte Homing Into Lymph Nodes: In Vitro Demonstration of the Selective Affinity of Recirculating Lymphocytes for High-Endothelial Venules," J. Exp. Med., 144, pp. 828-833 (1976) (copy enclosed) ("[Lymphocytes] ... did not bind to the flat endothelium of cortical capillaries, medullary venules or lymphatic sinuses" (page 829)). Thus, Holzmann's conjecture that VLA4 could be involved in lymphocyte adhesion to Peyer's patch HEV would not suggest to one of skill in the art that VLA4 was involved in the adhesion of lymphocytes to any other endothelial cells in any other organs or tissues.

Thus, nothing in Holzmann, either alone or when combined with the other cited documents, would motivate one of skill in the art to evaluate the ability of anti-$\alpha_4\beta_1$ antibodies to inhibit lymphocyte adhesion to non-HEV endothelial cells with a reasonable expectation of success in producing applicant's invention.

In view of the above, applicant requests withdrawal of the rejections and reconsideration and allowance of the pending claims.

Statement Under 37 C.F.R. §§ 1.56 and 1.97

Pursuant to 37 C.F.R. §§ 1.56 and 1.97, applicant makes of record the following documents, copies of which are submitted herewith:*

United States Patent 4,578,079 (Ruoslahti et al.), issued March 25, 1986;

Berlin, C. et al., "$\alpha_4\beta_7$ Integrin Mediates Lymphocyte Binding To The Mucosal Vascular Addressin MAdCAM-1," Cell, 74, pp. 185-195 (1993);

Dustin, M.L. and T.A. Springer, "Lymphocyte Function-associated Antigen-1 (LFA-1) Interaction with Intracellular Adhesion Molecule 1 (ICAM1) is One of at Least Three Mechanisms for Lymphocyte Adhesion to Cultured Endothelial Cells," J. Cell Biol, 107, pp. 321-333 (1988).

Erikson, H.P. et al., "Fibronectin Molecule Visualized In Electron Microscopy: A Long, Thin, flexible Strand," J. Cell Biol., 91, pp. 673-678 (1981);

Harlan, "Leukocyte-Endothelial Interactions," Blood, 65, pp. 513-525 (1985).

Knapp, Leukocyte Typing IV: White Cell Differentiation Antigens, 1989 Inst. for Immunology, University of Vienna 1087;

Marcantonio, E.E. and R.O. Hynes, "Antibodies to the Conserved Cytoplasmic Domain of the Integrin ß-1 Subunit React With Proteins in Vertebrates, Invertebrates and Fungi," J. Cell Biol., 106, pp. 1765-1772 (1988)

Osborn, L. et al., "Direct Expression Cloning of Vascular Cell Adhesion Molecule 1, a Cytokine-Induced Endothelial Protein That Binds to Lymphocytes," Cell, 59, pp. 1203-1212 (1989)

Ruoslahti, "Fibronectin and Its Receptors," Am. Rev. Biochem., 57, pp. 375-413 (1988)

Stamper, H.B. and J.J. Woodruff, "Lymphocyte Homing Into Lymph Nodes: In Vitro Demonstration Of The Selective Affinity Of Recirculating Lymphocytes for High Endothelial Venules," J. Exp. Med., 144, pp. 828-833 (1976);

Takada, Y. and M.E. Hemler, "The Primary Structure of the VLA-2/Collagen Receptor α_2 Subunit (Platelet GPIa): Homology to Other Integrins and the Presence of a Possible Collagen-binding Domain," J. Cell Biol., 109, pp. 397-407 (1989)

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* A completed Form PTO-1449, listing these documents, is attached hereto.

Applicant requests that the cited documents be (1) fully considered by the Examiner during the course of examination of this application and (2) printed on any patent issuing from this application.

This statement is being submitted after the mailing of a first Office Action on the merits. Applicant has paid the fee required under 37 C.F.R. §§ 1.97 and 1.17(p).

Respectfully submitted,

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I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON D.C. 20231, on September 18, 1995

Thomas Quinones
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